REMARKS

At the outset, Applicants wish to thank Examiners Rooney and Haddad for taking the time to discuss the outstanding office action and Applicants' proposed response with Applicants' representative. Applicants submit that the instant remarks not only address the grounds of rejection set forth in the outstanding Non-Final Rejection of October 6, 2008 but also the concerns raised by the Examiners in the course of the interview of February 23, 2009 and suggestions set forth therein. In particular, in an effort to expedite prosecution and simplify the issues at hand, Applicants have herewith canceled claims 38-40, incorporating the subject matter therefrom into independent claim 1. In that the subject matter now set forth in claim 1 was formerly presented in claims 38-40, Applicants respectfully submit that no new matter has been added. However, Applicants reiterate that this amendment is presented solely for the purpose of expediting prosecution and should not be construed as Applicants' agreement with or acquiescence to the grounds of rejection previously set forth.

Thus, claim 1 as amended is directed isolated allergen consisting of a polypeptide capable of binding to IgE antibodies from an individual being allergic against mugwort pollen, said polypeptide consisting of (a) the amino acid sequence of SEQ ID NO:1, (b) the amino acid sequence extending between residues 21 and 180 of SEQ ID NO:1, or (c) the amino acid extending between residues 181 and 396 of SEQ ID NO:1. Applicants respectfully submit that the allergens encompassed by the present claims, as well as the pharmaceutical compositions and diagnostic kits associated therewith, are not only described and enabled by the instant specification but are further novel and non-obvious over the prior art of record. Accordingly, Applicants respectfully submit that the instant response renders moot the outstanding claim rejections and places the instant application in condition for allowance. Further to this position, Applicants submit the following remarks:

Rejections Under 35 USC 112, First Paragraph

Enablement & Written Description:

Claims 1, 4, 15, and 18 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement and written description requirements. While the Examiner finds the specification to describe and enable an allergen consisting of SEQ ID NO:1 (claim 38), consisting of amino acids 181 to 396 of SEQ ID NO: 1 (claim 39), and consisting of amino acids 21 to 180 of SEQ ID NO:1 (claim 40), as well as compositions and kits thereof, she continues to find claims to allergen polypeptides comprising such sequences to lack enabling support and written description in the as-filed specification.

Applicants respectfully disagree with the Examiner's position for reasons of record. Nevertheless, in an effort to expedite prosecution, Applicants have amended the claims to be commensurate with the admitted scope of enablement and written description (i.e., replaced "comprising" with "consisting". Accordingly, Applicants respectfully petition for the reconsideration and withdrawal of the outstanding rejections under 35 U.S.C. § 112, first paragraph.

Rejections Under 35 USC 102

The Examiner reiterated the rejections of claims 1, 4, 15 and 38 under 35 U.S.C. § 102(b) as being anticipated by one or more of **Nilsen** et al., **Brandys** et al., **Hirschwehr** et al., **De La Hoz** et al., **Katial** et al., and **Paulsen** et al., noting that it remains her position that the cited prior art references disclose "an approximately 44 kDa polypeptide allergen in mugwort (*Artemisia vulgaris*) pollen" that appears to be identical to Applicants' "Art v 6" protein (SEQ ID NO: 1), a protein described by GenBank Accession Number AY904433 as having a molecular weight of approximately 44 kDa by SDS-PAGE.[1]

For reasons of record, Applicants continue to reject the Examiner's suggestion that the burden is on Applicants to show that the presently claimed allergen (SEQ ID NO: 1) is **not** identical to any of the allergens of the cited prior art or *vice versa*. In the previous office action,

[1] Applicants wish to point out that Applicants' SEQ ID NO: 1 has 1535 bp and is not in fact identical to the sequence set forth in GenBank Accession Number AY904433 (1513 bp). Moreover, the actual molecular weight of Applicants' SEQ ID NO: 1 (Art v 6) is 40.9 kDa and not 44 kDa as suggested by the Examiner.

Examiner admits that "[n]o sequence information is provided to unequivocably prove that any of the isolated polypeptides is indeed identical to At v 6 [sic]". However, she is satisfied with the fact that none of the information provided unequivocably proves that the isolated proteins of the prior art are **not** the recited Art v 6 of SEQ ID NO: 1. Applicants respectfully submit that the Examiner has a fundamental misunderstanding of the doctrine of inherency and the respective burdens arising therefrom.

Under the principle of inherency, **anticipation may not be established by probabilities or possibilities** ("A prior art event cannot be established based on speculation, or where a doubt exists." *Ethyl Molded Product Co. v. Betts Package, Inc.*, 9 USPQ 2d 1001, 1032-33 (E.D.KY 1988). Rather, the doctrine of inherency is available **only** when the prior inherent event can be established with **certainty**. The Court of Appeals for the Federal Circuit ("CAFC") closely follows this doctrine, finding inherent anticipation only when an alleged inherent fact is "**necessarily present**" in the prior art, and not merely sometimes, occasionally, or possibly present.[2] Thus, for a claimed product to be characterized as inherently disclosed, it must be a "**natural result flowing from the operation as taught**" in the prior art. *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (Fed. Cir. 2005). Importantly, when relying upon the theory of inherency, it is the Examiner's burden to provide facts or reasoning that reasonably support the determination that the allegedly inherent characteristic **necessarily** flows from the teachings of the applied prior art. *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). In other words, the evidence must make clear that the missing descriptive matter is **necessarily present** in the thing described in the reference. Inherency, however, may not be established by probabilities or possibilities. Accordingly, the "mere fact that a certain thing **may result** from a given set of circumstances **is not sufficient"**. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999), emphasis added. Likewise, the suggestion that a certain result or characteristic **may occur** or be present in the prior art **is not sufficient** to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); see also *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ

[2] See DONALD S. CHISUM, CHISUM ON PATENTS § 3.03 (2004); see generally Steven C. Carlson, Inherent Anticipation, 40 IDEA 297 (2000); Bradford J. Duft & Eric P. Mirabel, Principles of Inherency, 77 J. PAT. & TRADEMARK OFF. SOC'Y 539 (1995).

323, 326 (CCPA 1981). In sum, **inherency must be a necessary result and not merely a possibility**.

Thus, contrary to the Examiner's suggestion, the burden of "unequivocable proof" lies not with Applicants but with the Examiner, who must prove that the claimed invention is a "**necessary and inevitable**" consequence of the disclosure in a prior art reference. See *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F. 3d 1373, 1375 (Fed. Cir. 2003). As discussed previously and hereinbelow, not only is Applicants' claimed mugwort pollen allergen "Art v 6" of SEQ ID NO: 1 **not certainly, necessarily, and inevitably** present in the prior art disclosures but, given the ample rebuttal of record, substantial doubt exists as to its presence at all. While the Examiner repeatedly states that the approximately 44 kDa protein of the prior art is the claimed allergen "absent evidence to the contrary", Applicants respectfully submit that prosecution history is replete with "evidence to the contrary", facts, data, and expert opinion that substantially undermine the Examiner's suggestion that the various prior art protein bands extracted from mugwort pollen are identical to and therefore inherently anticipate Applicants' claims to the allergen of SEQ ID NO: 1.

Nevertheless, in an attempt to conclusively demonstrate that the claimed allergen peptide is **not** ***"necessarily present"*** in the prior art disclosures, Applicant submitted comparative data that raised significant doubts as to the validity of the Examiner's unwavering yet unsubstantiated assertions of inherent anticipation. In particular, Applicants submitted a listing of several potentially allergenic proteins having molecular weights ranging of 40 to 44kDa found to coexist in mugwort pollen extract (See Appendix B to the July 25th declaration of Dr. Ferreira). Setting aside Art v 6 (SEQ ID NO: 1) of the present invention, four of the eight proteins isolated from the 40-44kDa band of the mugwort pollen extract and described in Appendix B are known to possess allergenic activity. In particular:

- Phosphoglyercerate kinase (Calculated MW of 42.3) has been identified as an allergen in the fungus *Epicoccoum purpurascens* (Kukreja et al., 2008);
- Enolase (Calculated MW of 47.8) has been identified as an allergen in latex as well as in several fungi (*Cladosporium*, *Alternaria*) as well as yeast (Posch et al., 1997);
- Fructose bisphosphate aldolase (Calculated MW of 38.4) has been identified as a known food allergen found in wheat flour (Baur et al., 1998); and

- Malate dehydrogenase (Calculated MW of 35.5) has been identified as an allergen in the yeast *Malassezia furfur* (Onishi et al., 1999).

Accordingly, the "approximately 44 kDa" proteins identified in the cited prior art references are just as likely be one of these four known allergen proteins as they are to be Applicants' SEQ ID NO: 1. Thus, Applicants respectfully submit that the requisite certainty is noticeably absent from the instant case of inherent anticipation.

The Examiner dismissed the previously evidence on the grounds that there was no showing that these proteins are recognized by IgE or serum of mugwort-pollen allergic patients as described in the prior art, summarily disregarding Dr. Ferreira's expert opinion that "**it can be presumed with high certainty that these 4 enzymes are also allergens in mugwort due to their high evolutionary sequence conservation**." (See point 9 of the July 25, 2009 declaration of Dr. Fatima Ferreira). However, the degree to which a single allergen may cross-react with allergens from other species, even other families, is borne out by Applicants' Exhibit One, an article by Patricia Barral, et al. (J. Immunol., 2004, 172:3644-3651), a copy of which is provided herewith. Barral et al. demonstrate that an allergen from olive tree pollen, Ole e 10, shares IgE B cell epitopes with proteins from other allergen sources, including *Oleaceae*, *Gramineae*, *Betulaceae*, *Chenopodiaceae*, *Cupressaceae*, *Ambrosia*, and *Parietaria* pollens, latex, and vegetable foods, such as tomato, kiwi, potato, and peach, indicating that Ole e 10 is a pan-allergenic plant protein that shows notable intra- and interspecie IgE cross reactivity. Applicants also direct the Examiner's attention to their Exhibit Two, an article by Rosa Sanchez-Monge, et al. ("Chapter 6: Can cross-reactivity studies enable generic allergy prevention", Allergy Matters, Ed. Ludd et al., Vol. 10, March 2005), the first line of which reads "**The occurrence of homologous proteins in foods, pollen and latex is the molecular basis of the plant sources' allergenic cross-reactivity**." Thus, one would reasonably expect, at a minimum, that a known latex allergen (i.e., enolase) and a known food allergen (i.e., wheat flour allergen fructose bisophosphate aldolase) would cross-react with IgE from other allergen sources, such as IgE or serum of mugwort-pollen allergic patients, particularly when such allergens are isolated from a mugwort pollen extract. Accordingly, Applicants reiterate that the various "approximately 44 kDa" proteins described by the prior art have only a one in five chance of being Applicants' SEQ ID NO:1. Again, since the requisite certainty is noticeably absent, the prior art disclosures cannot

be fairly characterized as inherently anticipating the invention of the pending claims.

Additional factors that cast doubt on the Examiner's suggestion of inherency are as follows:

With regard to **Nilsen**, the Examiner specifically points to the "approximately 44 kDa" (actually ~43 kDa) bands found in lanes C, E, F, and K of Figure 1, as well as the disclosures in Table 1. However, of the proteins that might be characterized having a molecular weight of approximately 40.9 kDa (i.e., those having MW of 34, 39, 42, and 48 kDa), two showed no virtually no reactivity with IgE from mugwort patient serum (MW 34, 48 kDa). Although the remaining two bound IgE from 94% of the patients tested, they demonstrated only weak to medium radio-staining (MW 39 and 42 kDa), which suggests either a weak affinity for mugwort patient IgE and/or a lack of specific binding to mugwort patient IgE. In contrast, Applicants' Art v 6 of SEQ ID NO: 1 (MW 40.9 kDa) has been shown to be significantly less common in the population, binding only 36%[3] to 49.4%[4] of mugwort patient IgE. Given the divergence in prevalence, there is no reason to believe that either of Nilsen's doublet band proteins (i.e., the 39,000 or the 42,000 kDa protein) is identical to Applicants' SEQ ID NO: 1.

With regard to **Brandys**, the Examiner points to the "approximately 44 kDa" (actually ~43 kDa) bands found in lanes v, c, s, and p of Figure 2C. However, Applicants wish to point out that only lane "v" corresponds to mugwort pollen (*Artemisia vulgaris*); lanes c, s, and p correspond to other Artemisia species (*A. campestris*, *A. scoparia*, and *A. princeps*) and are therefore irrelevant to the present inquiry. In any event, like Nilsen, Brandys observed that the 40-42 MW extract isolated from mugwort pollen extract bound a "significant majority" of mugwort patient IgE (8 of 10), though with weak affinity (see Table 2). As noted above, Applicants' Art v 6 of SEQ ID NO: 1 (MW 40.9 kDa) is less significantly common, binding only 36% to 49.4% of mugwort patient IgE. Furthermore, Brandys observed the IgE component(s) found in *Artemisia vulgaris* to have a pI on the order of 4.55 (see Figure 3B), which is completely inopposite to Applicants' SEQ ID NO: 1 with a pI of 8.27. Given these critical distinctions, there is no reason to believe that the 43 kDa mugwort pollen extract protein identified by Brandys is identical to Applicants' SEQ ID NO: 1.

[3] See allergenicity data at http://www.allergen.org/Allergen.aspx.
[4] See Applicants' specification at p. 27.

With regard to **Hirschwehr**, the Examiner points to the "approximately 44 kDa" (actually ~46 kDa) bands found in lanes 10, 11, and 13 of Figure 1A and lanes 6 and 7 of Figure 3A, and patients A & B of Figure 5, patients A & B. However, like Nilsen and Brandys, Hirschwehr characterized the 46kDa fraction as a "prominent IgE-binding band" detected in mugwort pollen extract "by most of the sera". See p. 199, col. 2 at bottom. In contrast, Applicants' Art v 6 of SEQ ID NO: 1 (MW 40.9 kDa) is less significantly prevalent in the population, binding only 36% to 49.4% of mugwort allergic patient IgE. Thus, there is no reason to believe that the 46 kDa mugwort pollen extract protein identified by Brandys is identical to Applicants' SEQ ID NO: 1.

With regard to **De la Hoz**, the Examiner points to the "approximately 44 kDa" (actually ~42.7 kDa) bands found in lanes A and B of Figure 3 and lanes A, B, and C Figure 4. Like Nilsen, Brandys, and Hirschwehr, De la Hoz observed that the approximately 42.7 kDa mugwort protein, incorrectly dubbed "Art v 1", bound IgE from 68% of the patients tested (see Table 2). As noted above, Applicants' Art v 6 of SEQ ID NO: 1 (MW 40.9 kDa) is less significantly prevalent in the population, binding only 36% to 49.4% of mugwort allergic patient IgE. In addition, the De la Hoz "Art v 1" protein is an acidic protein with a pI of 4.4 and a denaturing (SDS-PAGE) molecular weight of approximately 60 kDa whereas Applicants' "Art v 6" protein is a basic protein with a pI of 8.27 and a denaturing (SDS-PAGE) molecular weight of approximately 40 kDa. Contrary to the Examiner's suggestion, these completely inopposite parameters are not merely experimental "discrepancies" but conclusive proof that the "Art v 1" mugwort pollen extract protein identified by De la Hoz is **not** the "Art v 6" protein of SEQ ID NO: 1.

With regard to **Katial**, the Examiner points to the "approximately 44 kDa" (actually ~45 kDa) band found in the AV lane of Figure 5. However, in that Katial used as their source of IgE antibodies pooled sera collected from 9 of 24 patients with 4+ ELISA to at least one species of Artemisia (see p. 341, col. 2), there can be no suggestion that the ~45 kDa mugwort extract protein identified by Katial is "capable of binding to IgE antibodies from an individual being allergic against mugwort pollen" as the pending claims require. Thus, in that the Katial reference fails to disclose or suggest each and every element of the pending claims, it cannot serve to anticipate the instantly claimed invention.

Finally, with regard to **Paulsen**, the Examiner specifically points to the "approximately 44 kDa" (actually ~45 kDa) fractions depicted in Figures 6A and B as well as the disclosures in Table I. However, like Katial, Paulsen fails to demonstrate that the approximately 45 kDa is "capable of binding to IgE antibodies from an individual being allergic against mugwort pollen" as required by the pending claims. According to Paulsen, while 18 antigens present in the extract bound anti-rabbit serum (a group which presumably includes the ~45 kDa protein), only 7 of these bound human IgE towards mugwort. See p. 211, col. 1 as well as data Figure 4. Applicants respectfully submit that there is no conclusive evidence that the approximately 45 kDa protein falls into this latter group of proteins binding human IgE. Furthermore, given that only anodic antigens are described in the CIE/CRIE results and that Applicants' ~40 kDa Art v 6 protein migrates to a cathodic pI of 8.27, it is more likely that it is **not** among Paulsen's group of seven IgE binding proteins. In any event, in that the Paulsen reference fails to disclose or suggest each and every element of the pending claims, it cannot serve to anticipate the instantly claimed invention.

In sum, Applicants respectfully submit that since the cited prior art references fail to **necessarily**, **inevitably**, and with **certainty** describe each and every claimed element, namely an allergen consisting of SEQ ID NO: 1 that binds mugwort patient IgE antibodies, they likewise fail to inherently anticipate the invention of the pending claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of the anticipation rejections of claim 1, 4, and 15 in view of the amendments and remarks herein.

Rejections under 35 U.S.C. § 103

The Examiner reiterated the rejection of claim 18 under 35 U.S.C. § 103(a) for being obvious over Nilsen et al., Brandys et al., Hirschwehr et al., De La Hoz et al., Katial et al., or Paulsen et al., further in view of USPN 4,459,360. According to the Examiner, US '360 cures the deficiencies of Nilsen et al., Brandys et al., Hirschwehr et al., De La Hoz et al., Katial et al., and Paulsen et al. by disclosing a diagnostic kit for mugwort allergy screening. The Examiner thus concludes that it would have been obvious to one of ordinary skill in the art to package the allergens of the prior art in a kit as taught by US '360.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See M.P.E.P. § 2142, 2143.

Applicants respectfully submit that US '360 fails to cure the above-noted deficiencies of the Nilsen et al., Brandys et al., Hirschwehr et al., De La Hoz et al., Katial et al., and Paulsen et al., namely the disclosure of an allergen consisting of SEQ ID NO: 1 that binds mugwort patient IgE antibodies. Thus, in that the prior art references, alone or in combination, fail to teach or suggest all the claim limitations, Applicants respectfully submit that the Examiner has failed to set forth a *prima facie* case of obviousness. Accordingly, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection of claim 18 in view of the amendments and remarks herein.

CONCLUSION

The outstanding Office Action set a three-month shortened statutory period for response, response being due on or before **January 6, 2009**. In that the Petition for a Two-Month Extension of Time extends this deadline to on or before **March 6, 2009**, Applicants respectfully submit that this response is timely and no additional fee is required. However, in the event that further fees are required to enter the instant response and/or maintain the pendency of this application, the Commissioner is authorized to charge such fees to our Deposit Account No. 50-2101.

If the Examiner has any questions or concerns regarding this communication, she is invited to contact the undersigned.

Respectfully submitted,

Date: /March 6, 2009/

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